

**BIOGRAPHICAL SKETCH**

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NAME: Ratna K Vadlamudi

POSITION TITLE: Professor

eRA COMMONS USER NAME (credential, e.g., agency login): rvadlamu

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
P.K.V. University, Maharashtra, India	B.S.	1981	Biology
Univ. Wyoming, Laramie, WY	M.S.	1991	Food Sci & Nutrition
Univ. Wyoming, Laramie, WY	Ph.D.	1994	Molecular Biology
Harvard Medical School/Dana Farber Cancer Ins	Post Doc	1997	Molecular Biology of Cancer
University of Texas MD Anderson Cancer Center, Houston, TX.	Post Doc	1999	Breast Cancer

**A. Personal Statement**

I have training in molecular biology, endocrinology, cancer biology, and have significant experience in the cancer preclinical models for testing of biologic, small molecule and endocrine agents. I use breast, ovarian and GBM cancer models for my research. As a postdoctoral fellow at DFCI/Harvard Medical School and as a junior faculty at UT MD Anderson Cancer Center, I have acquired significant experience relating to breast cancer research methods and models. As a PI or Co-Investigator on several university- and NIH-funded grants, I expanded my research to include preclinical models and Tg-mouse models for breast cancer research. My current research interests include characterizing the role of novel oncogenes / tumor suppressors in breast cancer initiation, progression and therapy resistance and identifying new molecular agents for therapeutic intervention and for early detection of cancer. During this time, I have served as PI of several NIH, CPRIT, DOD and private foundation grants and served in several study sections including NIH. During my tenure as a faculty, I have successfully trained 20 pre/post-doctoral fellows and 12 undergraduate/MD students as primary mentor. I have the expertise, leadership and motivation necessary to successfully train students. My past training, research experience, qualifications makes me particularly well-suited to participate as a mentor of the Xiangya Medical Student Research Program.

- a. **Vadlamudi RK**, Bagheri-Yarmand R, Yang Z, Balasenthil S, Nguyen D, Sahin AA, den Hollander P, Kumar R. Dynein light chain 1, a p21-activated kinase 1-interacting substrate, promotes cancerous phenotypes *Cancer Cell* 2004;5:575-585.
- b. Roy S, Chakravarty D, Cortez V, Mukhopadhyay KD, Bandyopadhyay A, **Ahn JM**, **Raj GV**, Tekmal RR, Sun LZ, **Vadlamudi RK**. Significance of PELP1 in ER-Negative Breast Cancer Metastasis. *Mol Cancer Res*. 2012 Jan;10(1):25-33 PubMed PMID: 22086908.
- c. Roy S, Gonugunta VK, Bandyopadhyay A, Rao MK, Goodall GJ, Sun L, **Tekmal RR** and **Vadlamudi RK**. Significance of PELP1/HDAC2/miR-200 regulatory network in EMT and metastasis of breast cancer. *Oncogene* 2014 Jul 10;33(28):3707-16. PMID: 23975430.
- d. Krishnan SR, Nair BC, Sareddy GR, Saha Roy S, Natarajan M, Suzuki T, Peng Y, **Raj G**, and **Vadlamudi RK**. Novel role of PELP1 in regulating a chemotherapy response in MTP53-expressing TNBC cells. 2015, *Breast Cancer Research and Treatment*, 150(3):487-99.

**B. Positions and Honors****Positions**

- 1999-03 Assistant Professor, Department of Molecular and Cellular Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.
- 2003-04 Associate Professor, Department of Molecular and Cellular Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.
- 2004-05 Associate Professor, Department of Genetics, Medical School, Louisiana State Health Sciences Center, New Orleans, LA
- 2006-10 Associate Professor, Department of Obstetrics and Gynecology, Medical School, University of Texas Health Sciences Center, San Antonio, TX
- 2007- Faculty Member, Cancer Therapy and Research Center, NCI designated Cancer Center
- 2008- Faculty Member, The Integrated Multidisciplinary Graduate Program (IMGP-PHD program) Tracks: Cancer Biology, Cellular and Molecular Biology, Molecular medicine, University of Texas Health Sciences Center, San Antonio, TX.
- 2010- **Professor (with Tenure)**, Department of Obstetrics and Gynecology, Medical School, University of Texas Health Sciences Center, San Antonio, TX.

**Awards and Honors:** 1980-81, Raman Scholarship, BS program; 1981, ASPEE Gold Medal for securing Highest Grade point average during undergraduate program; 1991, Graduate Research Assistantship, University of Wyoming; 1991, Gamma Sigma Delta Honor Society (Biological Sciences); 1995, Outstanding Dissertation Award (Biological Sciences); 2001, DOD Concept grant award; 2006, First NIH RO1 grant award; 2006, DOD Concept grant award; 2008, DOD Idea award; 2009 AACRMSI Faculty Scholar in Cancer Research award; 2009, Susan G. Komen Foundation Individual Investigator grant award; 2010, AACRMSI Faculty Scholar in Cancer Research award. 12/2012, Associate Editor, BMC Cancer; 2015, UTHSCSA/CTRC Discovery of the Year; **2015, AAAS Fellow**-elected for distinguished contributions to the field of molecular biology

**Study Sections:** 2001- 2003, Member-Cell Bio I Section, DOD BCRP; 2003-2005, Member-Tumor Cell Bio II Section, Komen Foundation; 2006-2009, Member-DOD BCRP; 2008, 2009- present: Adhoc Member -NIH Cancer drug development and therapeutic SBIR/STTR; 2010-2011:Member-Diagnosis section, California Breast Cancer Research Foundation; 2010: Member-Ovarian Cancer Study Section, DOD; 2010-2014: Member-Cancer Biology Section, Italian Ministry of Health (MOH); 2012: Member-DOD Ovarian Cancer Study Section-Diagnosis and Detection-Pathobiology; 2013-2014, NSF Graduate Research Fellowship Panel; 2014-2015, Member-DOD Breast Cancer Study Section; 2014-2015, Member-NCI SBIR/STTR; 2012-2016, Member-DMP study section, NIH, 2016-2018, **Chair**-DMP study section, NIH.

**Member:** 01/91-Present, Member, American Association for Advancement of Science; 01/94-Present, Member, American Society for Biochemistry and Molecular Biology; 01/96-Present, Member: American Association for Cancer Research; 12/11-Present, Member, Endocrine Society.

## C. Contributions to Science

1. My early publications directly examined the mechanism of growth factor signaling with a particular focus on discovering novel signaling cascades that are activated by growth factors and examined the mechanism(s) by which growth factors promote cell migration. This project lead to the identification of Pak1 as a target of heregulin/neuregulin signaling. I developed an inducible model cell line expressing kinase active Pak1 and demonstrated for the first time that Pak1 may have oncogenic functions. Using Yeast two hybrid screen, I have identified ten novel Pak1 interacting proteins. Some of the identified Pak1 interacting proteins such as Filamin and DLC1 allowed us to identify new signaling pathways by which growth factors promote cell survival and motility.
  - a. **Vadlamudi RK**, Adam L, Wang RA, Mandal M, Nguyen D, Sahin A, Chernoff J, Hung MC, Kumar R. Regulatable expression of p21-activated kinase-1 promotes anchorage-independent growth and abnormal organization of mitotic spindles in human epithelial breast cancer cells *J Biol Chem* 2000;275:36238-36244.
  - b. **Vadlamudi RK**, Li F, Adam L, Nguyen D, Ohta Y, Stossel TP, Kumar R. Filamin is essential in actin cytoskeletal assembly mediated by p21-activated kinase 1 *Nat Cell Biol* 2002 4:681-690.
  - c. **Vadlamudi RK**, Manavathi B, Singh RR, Nguyen D, Li F, Kumar R. An essential role of Pak1 phosphorylation of SHARP in Notch signaling *Oncogene* 2005 Jun;24(28):4591-4596.

- d. Chakravarty D, Nair SS, Santhamma B, Nair BC, Wang L, Bandyopadhyay A, Agyin JA, Brann D, Sun L, Yeh I, Lee FY, Tekmal R, Kumar R and **Vadlamudi RK**. Extranuclear functions of ER impact invasive migration and metastases of breast cancer cells. *Cancer Research*, 2010, 70(10):4092-101.
2. Estrogen contribute to the progression of breast cancer, and resistance to estrogen receptor (ESR1) targeted therapies is a major clinical problem. My research findings implicated growth factor signaling crosstalk with estrogen receptor signaling play an important role in cancer progression. My research discovered several novel coregulator (coactivators/corepressor) proteins including MTA1, PELP1, Pak1, MICOA, HRS, KDM1, ATF4 that play a key roles in ESR1 signaling cross talk and provided evidence that deregulated coregulator signaling contributes to resistance. These research findings led to the rational design of small organic molecule (ESR1 coregulator binding inhibitor, ECBI) that can emulate ESR1 coregulator binding in the structural context critical for ESR1. UT filed a patent on this discovery. These studies are funded by NCI and CPRIT and I served as the primary investigator.
  - a. Mazumdar A, Wang RA, Mishra SK, Adam L, Bagheri-Yarmand R, Mandal M, **Vadlamudi RK**, Kumar R. Transcriptional repression of oestrogen receptor by metastasis-associated protein 1 corepressor *Nature Cell Biol* 2001 Jan;3(1):30-37.
  - b. Kumar R, Wang RA, Mazumdar A, Talukder AH, Mandal M, Yang Z, Bagheri-Yarmand R, Sahin A, Hortobagyi G, Adam L, Barnes CJ, **Vadlamudi RK**. A naturally occurring MTA1 variant sequesters oestrogen receptor-alpha in the cytoplasm *Nature* 2002;418:654-657.
  - c. Barnes CJ, **Vadlamudi RK**, Mishra SK, Jacobson RH, Li F, Kumar R. Functional inactivation of a transcriptional corepressor by a signaling kinase *Nature Struct Biol* 2003 Aug;10(8):622-628.
  - d. Cortez V, Mann M, Tekmal S, Suzuki S, Miyata N, Rodriguez-Aguayo C, Lopez-Berestein G, Sood AK and **Vadlamudi RK**. Targeting PELP1-KDM1 axis as a potential therapeutic strategy for breast cancer. *Breast Cancer Research* 2012, 14:R108.
3. My research for the past 10 years has centered on the identification, cloning and characterization novel ER regulatory protein named proline (P), glutamic acid (E) and leucine (L) rich protein (P) 1 (PELP1), whose expression is commonly deregulated in several cancers including breast cancer. My research program made several key discoveries and established the molecular mechanisms by which PELP1 regulated ER signaling. My research findings established PELP1 as a potential oncogene and a novel therapeutic target. We designed a small molecular inhibitor of PELP1. UTHSCSA obtained patent for this molecule. This ongoing program is supported by NCI grant and I serve as primary investigator.
  - a. Rajhans R, Nair SS, Holden AH, Kumar R, Tekmal RR, **Vadlamudi RK**. Oncogenic potential of the nuclear receptor coregulator proline-, glutamic acid-, leucine-rich protein 1/modulator of the nongenomic actions of the estrogen receptor. *Cancer Research* 2007;67:5505-5512.
  - b. Nair BC, Nair SS, Chakravarty D, Rambabu C, Manavathi B, Yew RP, Tekmal RR, Kumar R and **Vadlamudi RK**. CDK-mediated phosphorylation plays a critical role in PELP1's oncogenic functions. *Cancer Research*, 70:7166-75, 2010.
  - c. Nair SS, Nair BC, Cortez V, Chakravarty D, Metzger E, Schüle R, Brann DW, Tekmal R, and **Vadlamudi RK**. PELP1 is a reader of Histone H3 methylation that facilitates ER target gene activation by regulating KDM1 specificity. *EMBO Reports*, 2010,11:438-44.
4. In collaboration with several investigators, I have developed and characterized six pre-clinical transgenic mice and conditional knockout mice models. I was extensively involved in (1) establishing Pak1 Tg mice and characterizing the molecular mechanisms of hyperplasia phenotype, (2) establishing ATF4 Tg mice, (3) developing PELP1 cyto mice and demonstrating a role of PELP1 mis-localization in therapy resistance, (4) establishing conditional PELP1 KO mice and demonstrating its role in stroke, (5) establishing forebrain specific aromatase knockout mice, and demonstrating the role of locally synthesized estrogen in neuronal survival, and (6) establishing an inducible TG mice for PELP1 and demonstrating its oncogene functions in vivo.
  - a. Wang RA, Mazumdar A, **Vadlamudi RK**, Kumar R. P21-activated kinase-1 phosphorylates and transactivates estrogen receptor-alpha and promotes hyperplasia in mammary epithelium *EMBO J* 2002, 21:5437-5447.
  - b. Rayala SK, Zhang H, Holm C, **Vadlamudi RK**, and Kumar R. Extracellular coactivator signaling confers insensitivity to tamoxifen *Clinical Cancer Research* 2009;15(4123).

- c. Cortez V, Samayoa C, Zamora A, Martinez L, Tekmal RR, **Vadlamudi RK**. PELP1 overexpression in the mouse mammary gland results in the development of hyperplasia and carcinoma. *Cancer Research*, 2014, 74:7395-405
  - d. Sareddy GR, Zhang Q, Wangde R, Scott E, Zou Y, O'Connor JC, Chen Y, Dong Y, \***Vadlamudi RK**, Brann DW. Proline-, Glutamic Acid-, and Leucine-Rich Protein 1 (PELP1) Mediates Estrogen Rapid Signaling and Neuroprotection in the Brain. *Proc Natl Acad Sci U S A*. 2015, 11/2015, doi: 10.1073/pnas.1516729112 \***Corresponding author**.
5. Estrogen has a wide range of actions in the brain including the improvement of cognitive functions, neuroprotection, and protection from brain tumors. My research past few years has centered on understanding the molecular mechanisms that contributes to estrogen mediated neuroprotection under conditions of stroke and prevention of brain cancer. I published several papers implicating the role of locally derived estrogen and role of ER co-regulatory proteins in estrogen mediated protective functions in brain. I served as PI and Co-PI of these NIH funded studies.
- a. Zhang QG, Han D, Wang RM, Dong Y, Yang F, **Vadlamudi RK**, Brann DW. C terminus of Hsc70-interacting protein (CHIP)-mediated degradation of hippocampal estrogen receptor- $\alpha$  and the critical period hypothesis of estrogen neuroprotection. *Proc Natl Acad Sci U S A*. 2011, 108:E617-24.
  - b. Sareddy GR, Nair BC, Gonugunta VK, Zhang QG, Brenner AJ, Brann DW, Tekmal RR, **Vadlamudi RK**. Therapeutic significance of estrogen receptor  $\beta$  agonists in gliomas. *Mol Cancer Ther*. 2012 11:1174-82.
  - c. Sareddy GR, Nair BC, Krishnan SK, Gonugunta VK, Zhang QG, Suzuki T, Miyata N, Brenner AJ, Brann DW, **Vadlamudi RK**. KDM1 is a novel therapeutic target for the treatment of gliomas. *Oncotarget*. 2013; 4(1):18-28.
  - d. Sareddy GR, Li X, Liu J, Viswanadhapalli S, Garcia L, Gruslova A, Cavazos D, Garcia M, Strom AM, Gustafsson JA, Tekmal RR, Brenner A, **Vadlamudi RK**. Selective Estrogen Receptor  $\beta$  Agonist LY500307 as a Novel Therapeutic Agent for Glioblastoma. *Sci Rep*. 2016 Apr 29;6:24185. PubMed PMID: 27126081.

#### Complete List of Published Work in My Bibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/ratna.vadlamudi.1/bibliography/42857741/public/?sort=date&direction=ascending>

#### Ongoing Research Projects:

<b>CPRIT DP150096 Bridging the Gap Award</b>	3/1/15 to 2/30/18	2.4 CM
ESR1 coregulator binding site inhibitors (ECBIs) as novel therapeutics to target hormone therapy resistant breast cancer.		
Total cost: \$1,992,460; <b>Role:</b> PI		
<b>NIH/NCI R01CA178499(MPI:Vadlamudi and Brenner)</b>	9/01/14 – 08/31/19	2.4 CM
Novel ER beta agonists for the treatment of gliomas		
Total cost: \$1,868,750.00; <b>Role:</b> PI		
<b>NIH/NCI 1R01CA179120-01A1 (MPI: Rao and Vadlamudi)</b>	2/1/15-1/31/20	0.96CM
miRNAs: Safe and effective therapeutic adjuvants for treating drug resistant TNBC.		
Total Cost: \$1,738,624.00; <b>Role:</b> MPI		
<b>NIH/NINDS R01NS088058-01A1 (MPI: Brann and Vadlamudi)</b>	2/1/15-4/31/20	1.2CM
Brain Aromatase in Neurological Function and Disease.		
Total cost: \$1,779,345.00; <b>Role:</b> MPI		
<b>DOD GRANT12046431 (PI:Tekmal)</b>	07/2016 - 06/2019	0.6 CM
Total Costs: \$1,069,500.00		
Prevention of breast cancer and therapy resistance using novel therapeutic approaches		
<b>Role:</b> Co-investigator		
<b>NIH/NCI R01 CA164122-01 (PI: Curiel)</b>	09/01/12-06/30/17	0.96CM
B7-H1 signaling in ovarian cancer		
Total cost: \$ 1,458,000; Goals: (1) Test the hypothesis that ERbeta signals augment B7-H1 blockade effects in cancer (2) Test the hypothesis that dysfunctional B7-H1 signaling in cancer is dendritic cell-dependent.		
<b>Role:</b> Co-investigator		

Description of project(s) the Xiangya student will be working on (limit 1 page). Student can participate in any of the following ongoing projects

**Project 1: Establish the mechanisms of ER $\beta$  mediated tumor suppression:** Glioblastoma (GBM) are the most malignant primary brain tumor and patients with GBM (grade IV glioma) have a survival time of approximately 14 months. Estrogen plays a crucial role during brain development and differentiation. Epidemiological and experimental evidence suggests tumor suppressive role of estrogen on brain tumors. However, the molecular mechanisms by which estrogen mediate protection against GBM remains unknown. Estrogen functions are mediated by two ER-subtypes: ER $\alpha$  that functions as tumor promoter and ER  $\beta$  that functions as a tumor suppressor. The central hypothesis is that ER $\beta$  agonists inhibit the growth of GBM by enhancing tumor suppressive functions of ER $\beta$  and that ER $\beta$  agonists promote differentiation of glioma stem cells leading to increased therapeutic efficacy. Research methods for this project include primary GBM cell culture, CRISPR/Cas9 models, isolation and culture of glioma stem cells, RTqPCR. Western, orthotopic xenograft assays, RNA-seq, ChIP, apoptosis assays and drug testing using in vitro and in vivo assays.

**Project 2: Development of novel drugs to treat therapy resistant breast cancer.** Breast cancer (BC) has several distinct molecular subtypes, including estrogen receptor (ESR1) positive and triple negative BC (TNBC). A significant proportion of ESR1-positive therapy sensitive-BCs (TS-BC) initially respond to antiestrogens or aromatase inhibitors, but become therapy resistant-BCs (TR-BC) and progress to incurable metastases. Further, TNBC subtype has a more aggressive clinical course and lack targeted therapies. Development of effective therapies for women with TR-BC and TNBCs represents the highest unmet need. Recent studies revealed the potential role of several members of the Nuclear Receptor (NR) superfamily as molecular drivers in TR-BC and TNBC. This project is aimed to develop first-in-class polyfunctional small molecules, ERXs that have activity in the TR-BCs and TNBCs. ERXs block NR and coregulator interactions. Research methods include culture of breast cancer cells, CRISPR/Cas9, cloning, RTqPCR. Western, Xenograft assays, lentivirus transductions, and IHC analysis of mice and human breast tumors.

**Project 3: Define the molecular mechanisms by which oncogene PELP1 contribute to breast cancer progression.** Proline-, glutamic acid-, and leucine-rich protein 1 (PELP1) is a scaffolding protein that functions as a coregulator of several transcription factors and nuclear receptors. PELP1 plays essential roles in several pathways including hormonal signaling, cell cycle progression, ribosomal biogenesis, and the DNA damage response. PELP1 expression is upregulated in several cancers, its deregulation contributes to therapy resistance, and it is a prognostic biomarker for breast cancer survival. This project will utilize PELP1 TG and PELP1 KO mice to establish the mechanisms by which PELP1 contribute to breast cancer progression and to develop small molecular inhibitor of PELP1. Research methods for this project include cancer cell culture, breeding of PELP1 TG/KO mice models, characterizing the phenotype, monitoring and collection of tumors, isolation and culture of cancer stem cells, apoptosis and migration assays, cell cycle analysis, Western and RTqPCR, whole mount analysis, mice surgeries, testing the effect of hormone and carcinogens on mammary tumor inductions, RNA-Seq and Chi-Seq of TG mice tissues, and Xenograft assays.

**Project 4: Brain Aromatase in Neurological Function and Disease.** Recent work has shown that the forebrain, in particular the hippocampus, exhibits high expression of aromatase (the 17 $\beta$ -estradiol (E2) synthesis enzyme) in both males and females, and has significant E2-generating capacity. Under basal conditions, aromatase is highly expressed in neurons, whereas after brain injury, aromatase becomes highly expressed in reactive astrocytes. Currently, the roles and functions of local-derived E2 in the forebrain are poorly understood. The objective of this project is to elucidate the role of brain-derived E2 in both physiological and pathological situations. This project will test the hypothesis utilizing novel mouse models with selective knockout of aromatase expression in forebrain neurons (FBN-ARKO $^{-/-}$ ) or in astrocytes (AS-ARKO $^{-/-}$ ). These studies will have a significant impact upon the field by elucidating the roles, mechanisms and control of brain-derived E2, and this will lead to generation of potential new therapies for neurological disorders. Research methods include characterizing conditional KO mice models, westerns blotting, RTqPCR, creating stroke conditions in mice, animal surgeries, collection of brain tissues, breeding of mice, behavior testing, RNA-Seq and global gene expression analysis, ChIP, and IHC analysis of brain tissues

**5. Other ongoing projects** include (1) establishing the role of ER  $\beta$  agonists in ovarian cancer (2) defining the role of epigenetic enzymes (KDM1, G9a) in breast cancer stem cell driven cancer progression (3) development of small molecule inhibitors of LIF for treating breast cancer (4) ER  $\beta$  agonist combination therapy for treating Ovarian cancer, and (5) effect of ERX combination therapy with CDK4/6 inhibitors.